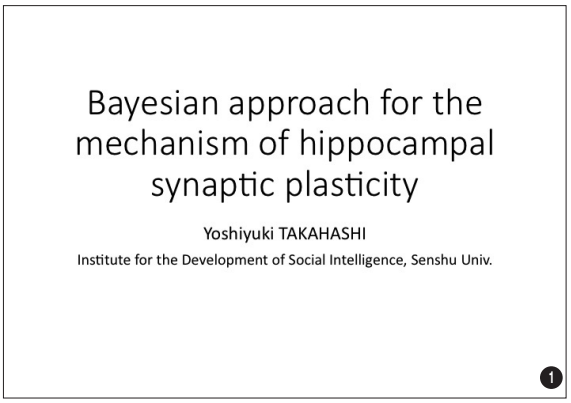
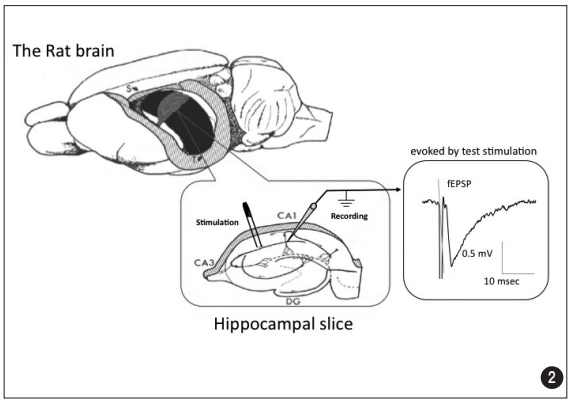
【研究報告1】

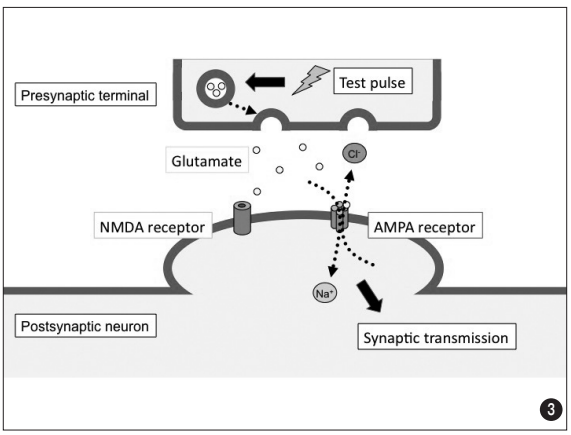
高橋　良幸（心理科学研究センター ポスト･ドクター）

“Bayesian approach for the mechanism of hippocampal synaptic plasticity”



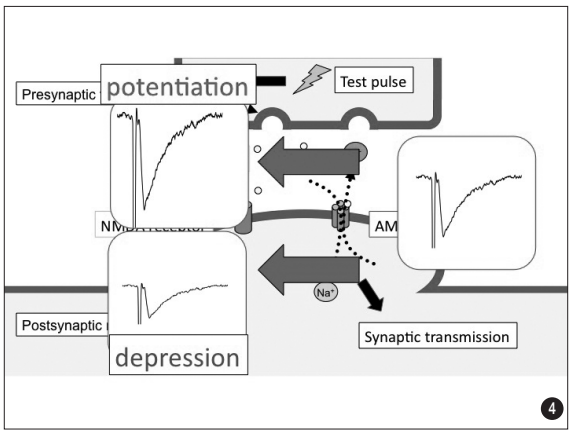


Hippocampal synaptic plasticity is one of the important candidates of physiological basis of learning and memory. Hippocampal slice is prepared from the rat brain and synaptic responses are recorded from the Hippocampal slice preparation. Test pulses are applied from the stimulation electrode, and the wave forms are recorded from recording electrode. The red line means the slopes of synaptic response. Traditionally we used this slope as an evaluation value of the strength of synaptic response. In the next slide, I will explain how to cause the synaptic response.

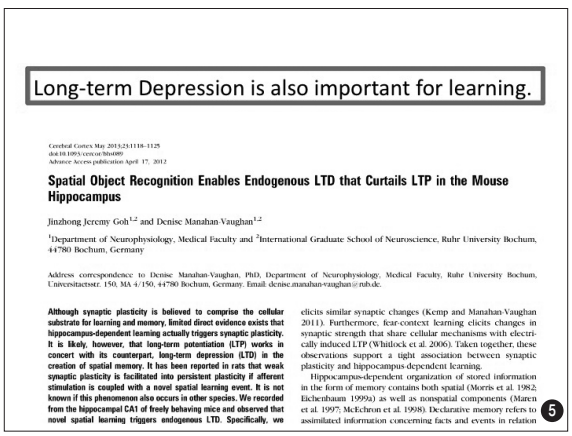


Presynaptic neuron is stimulated by test pulses. Neurotransmitter, glutamate was released from presynaptic terminal. Glutamate binds to those receptors. AMPA receptor

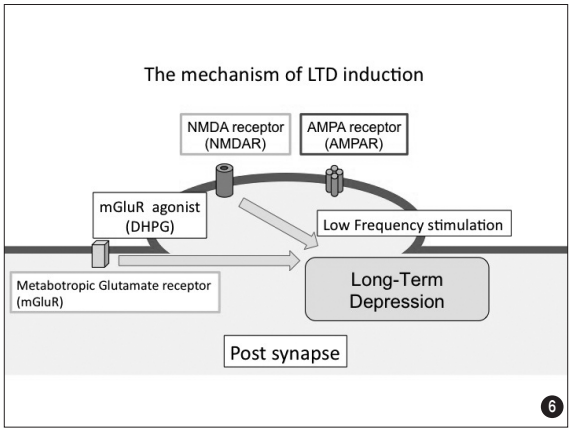
is one type of glutamate receptors. The ion channel of AMPA receptors will open by binding glutamate. Some ions influx to post-synaptic site, and efflux from post-synaptic neurons. Those ions transfer recorded as synaptic response.



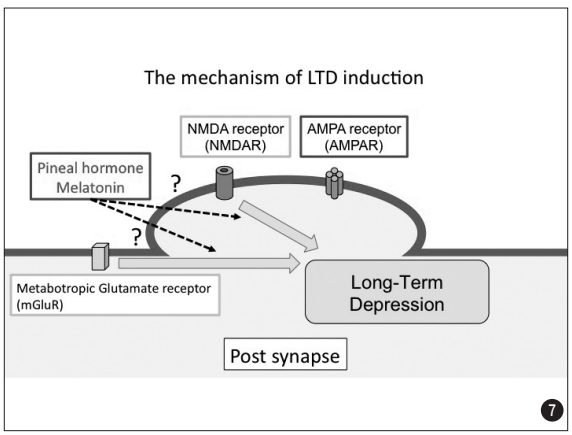
Some procedures potentiate or depress the synaptic response. Those potentiation and depression are called as synaptic plasticity. Synaptic plasticity is very important for learning and memory.



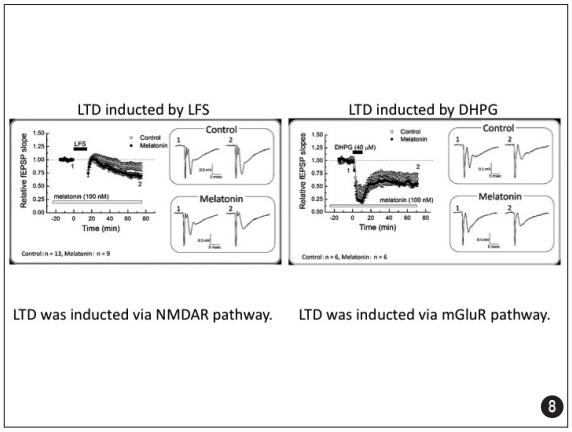
This paper was published last year. In this paper, electrodes were inserted hippocampus of a living rat. And synaptic responses were recorded from the free-moving rat. Synaptic responses have been depressed for a long time after some types of learning task. The authors indicated that long-term depression, LTD, might play an important role in some type of learning task.



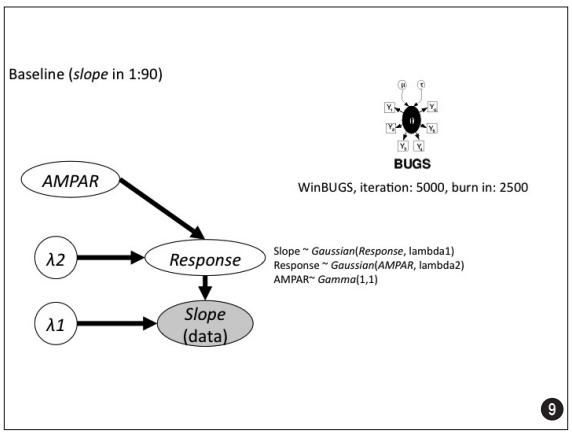
Slide #6 indicates the mechanisms of LTD induction. LTD is induced by two pathways. The one of the pathway is NMDA receptor-dependent pathway. NMDA receptor is another type of glutamate receptors. Metabotropic glutamate receptor-dependent pathway is another type of pathway. Low frequency stimulation may induce NMDA receptor-dependent LTD. And, metabotropic glutamate receptor-agonist, DHPG treatment may induce metabotropic glutamate receptor dependent LTD.



However, it is unclear that endogenous substances, which can regulate those two pathways. In this presentation, I focused on pineal hormone melatonin. Because it is reported that melatonin can regulate the learning performance.

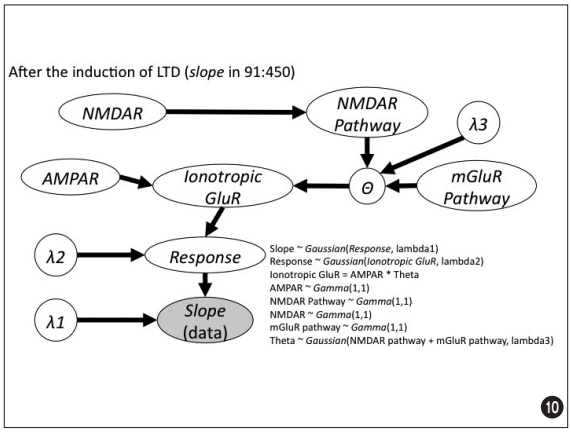


Slide #8 shows the measured data. Left figures indicate the result of NMDA receptor-dependent LTD. And Right figures indicate metabotropic glutamate receptor-dependent LTD. The open circle means control groups and black one means melatonin treatment groups. Horizontal axis indicates the time course of experiment and vertical axis means relative slopes of synaptic response. The waveforms indicate synaptic responses. Number 1, means just before the induction of LTD, and number 2 means after the induction of LTD. As you know, synaptic responses were depressed by those procedures. In this presentation, I estimated the parameters of synaptic response from those measured data.

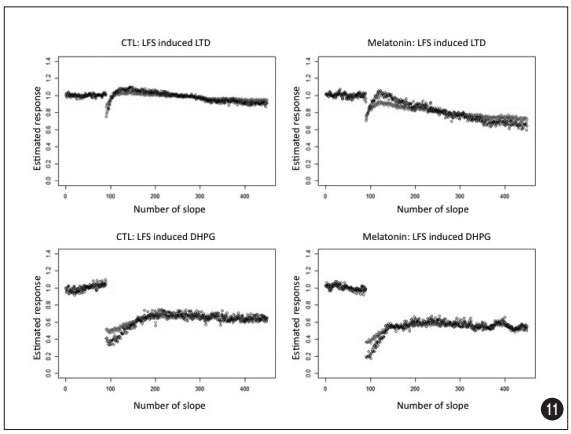


Data were analyzed by WinBUGS; iteration was 5,000 and burn-in 2,500. At first, I will explain the model before the LTD induction. The parameter ***Response*** follows a normal distribution. The average of this distribution is estimated from parameter *AMPAR*, and variance is *lambda 2*. *Lambda 1* and *2* are error term, follow a gamma distribution, and these are thought as non-informative prior distributions. *AMPAR* also followed non-

informative prior distribution. *Slope* is measured value, and follows a normal distribution, average is estimated from parameter *Response*, and variance is *lambda 1*.

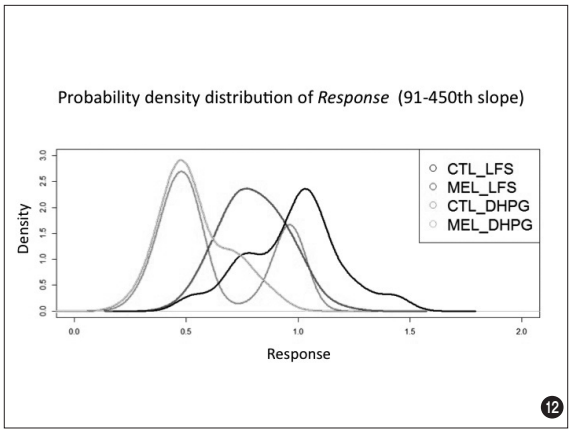


Slide #10 indicated the model after induction of LTD. NMDA receptor and metabotropic glutamate receptors were activated by each procedure of LTD induction. Parameters of those pathway follow the gamma distribution as non-informative prior distribution. Parameter *Theta* means synaptic plasticity power. *Theta* followed a normal distribution, location parameter is sum of NMDA receptor pathway and metabotropic glutamate receptor pathway. Scale parameter is *lambda 3*. *Response* follows Gaussian distribution. Location parameter of this distribution is *ionotropic Glutamate receptors*. *Response* follows location parameter is a product of *AMPAR* and *Theta* and scale parameter is *lambda 2*. *Slope* is measurement data and estimated from *Response*.

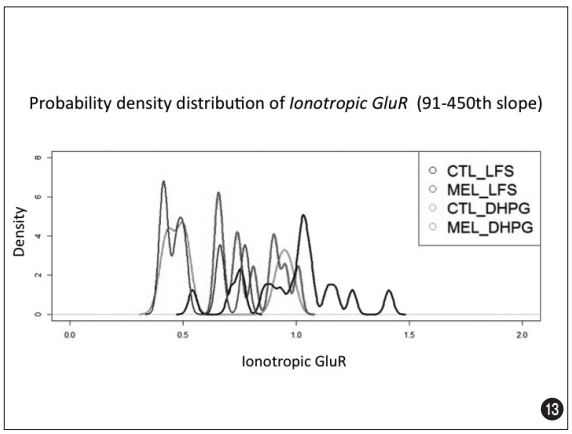


At first, we will check the result of estimated parameter *Response*. The figures indicate

the measured value as black circle and the average of the estimated parameter *Response* as red circle. Upper figures indicated NMDA receptor dependent LTD and lower figures indicate the metabotropic glutamate receptor-dependent LTD. As you see, synaptic responses were well established in all condition. It is important that the probability density distribution of parameter *Response* after the induction LTD.

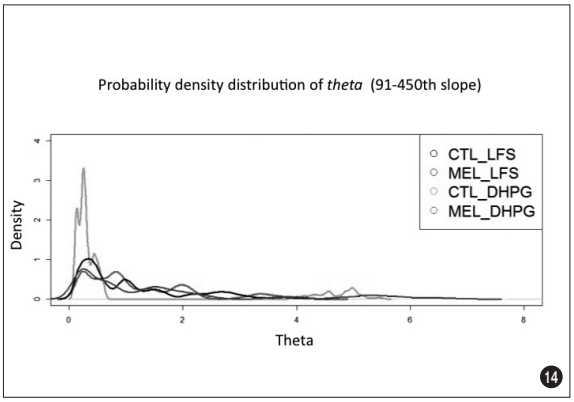


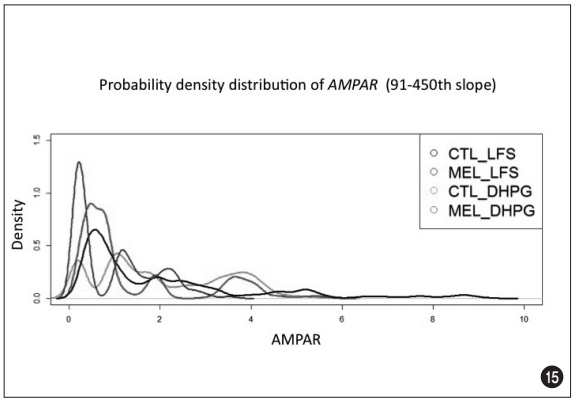
This is the probability density distribution of *Response* after LTD induction. In NMDA receptor-dependent LTD, control have peaks around 1, but melatonin treatment groups have a peak at the left side of control groups. Blue line and green line indicated the metabotropic glutamate receptor-dependent LTD conditions. In control group, the distribution has two peaks, but melatonin condition has one peak. And, melatonin treatment strongly depressed the synaptic response than control groups.



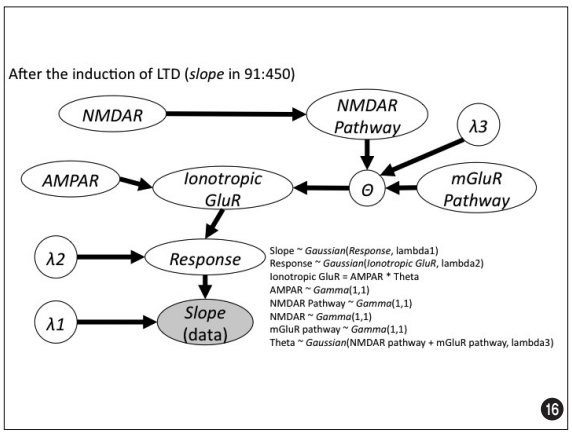
Parameter of *ionotropic Glutamate receptor* is a product of parameter *AMPAR* and *Theta*.

And *ionotropic Glutamate receptor* is a location parameter of prior distribution of *Response*. Slide #13 is a probability density distribution. In LFS-control group, the peak of probability is around 1, but melatonin group of LFS condition and both groups of DHPG condition shifted the peak left side.





Finally, probability density distribution of *AMPAR* and *Theta*. Only in control group of DHPG, peak of distribution was about 0.3 (slide #14). However, the melatonin group of DHPG, distribution has broad tails. This result indicates melatonin treatment affects parameter *Theta*. The posterior probability density distribution of *AMPAR* has a peak of around 0.3 in melatonin group of DHPG (slide #15). However, the distribution of control group in DHPG has a broad range. Those results indicated that melatonin attenuated ion transfer via AMPA receptors in LTD induction by DHPG application.



I have introduced the estimation results of those parameters in this model (slide #16).

However, as prior information, other parameters should be included in this estimation model. Such a firing rate of neuron itself and the introduction of those pathways and so on, Bayesian approach has unrevealed possibility in electrophysiology and physiological psychology, I think. Thank you.

Kensuke Okada

Thank you very much. His talk is about Bayesian estimation on the physiological data, so do you have any questions or comments. Please.

Questioner

For the estimation of a response, it seems that model do not quite fit with the data at the time of 100 or something. The first phase, not first but it seems that there is a rapid or abrupt change at 100 or around that, but around that the model does not fit well at the first stage but after that it fits very well (slide #11). Do you have any idea why that occurred?

Yoshiyuki Takahashi

I think that LTD have two phases. One phase is early, and the other one is late phase, but in this model, there are no time parameters, so I should include such as time course parameter in model.

Questioner

Okay, thank you.

Kensuke Okada

Other questions and comments? No. Well, I have one, but maybe it's time so I'll ask you a little later, so thank you very much.